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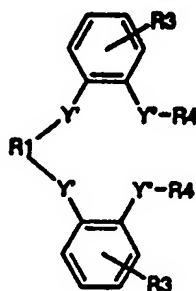
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A SENSOR PROVIDED WITH SUCH A COMPOUND OR MEMBRANE

(I)

## (57) Abstract

Disclosed is an anion-complexing compound (I) wherein R1 and A represent an aromatic 6-ring, Y' represents a -NHC(X)NH-group, and Y'' represents a rest selected from the group -NHC(X')-, -C(X')NH- and -NHC(X')NH-, wherein X and X', independently of one another, represent a sulphur or oxygen atom. R4, R4' are either identical representing a variety of groups, or together represent a group so that the compound has a macrocyclic structure. The invention also relates to a method of preparing such a compound, an ion-selective membrane as well as a sensor provided with such a compound or membrane.

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Anion-complexing compound, method of preparing the same, an ion-selective membrane and a sensor provided with such a compound or membrane

The present invention relates to an anion-complexing compound with the formula I of the formula sheet, wherein

R1 is a rest selected from the group of rests with the  
5 formulas II, III, and IV of the formula sheet; of which the ring may or may not be substituted with 1 to 3 R2 groups which may or may not be different from each other, wherein R2 represents alkyl or alkoxy;  
Y' represents a -NHC(X)NH-group, and  
10 Y" represents a rest selected from the group -NHC(X')-, -C(X')NH- and -NHC(X')NH-, wherein  
X and X', independently of one another, represent a sulphur or oxygen atom;

A represents an aromatic 6-ring which may or may not  
15 be substituted with 1 or 2 R3 groups, which R3 groups, independently of each other, represent alkyl, alkoxy, NO<sub>2</sub>, or a halide selected from the group consisting of fluorine and chlorine; and

R4, R4' are either  
20 a) identical, representing aryl that may or may not be substituted with 1 or 2 R3 groups, an alkyl, an acyl and an aryl sulphonyl which may or may not be substituted with 1 or 2 R3 groups;

or

25 b) together form a single rest, which rest is selected from the group of a rest with the formula V of the formula sheet, which may or may not be substituted with 1 or 2 R3 groups, and an alkyl group with the formula -(CH<sub>2</sub>)<sub>n</sub>- wherein n is 2 to 6.

30 Alkyl in the present application is to be understood to be a hydrocarbon rest which may or may not be branched, having a chain length of 1 to 15 carbon atoms. The term alkoxy is understood to mean an -OR group, wherein R is an alkyl as previously defined. Aryl is understood

to be a group according to formula V of the formula sheet, wherein R is as previously defined. An acyl group is understood to be -C(O)R or an -C(O)Ar, wherein R stands for alkyl and Ar for aryl, both as previously defined.

5 Nishizawa, S. et al (ref. 1) describe anion recognition by neutral urea and thiourea compounds with an anion-complexing activity. These compounds differ from the compounds according to the present invention in particular, through the smaller number of hydrogen bonds provided  
10 by the (thio)urea groups (2). As R1, which links the (thio)urea group, a rest derived from 1,3-bis(amino methyl) benzene is described.

Buehlmann P. et al. (ref. 2; same authors as ref. 1) have described neutral bis-(thio)urea compounds. The  
15 compounds differ from the compounds of the present invention in particular in the smaller number of hydrogen bonds provided by the (thio)urea groups (2). Also described as R1, which binds the (thio)urea groups, is a 2,7-di-tert.-butyl-9,9-dimethyl-4,5-xanthene diamine-derived rest.

20 Nishizawa, S. et al. (ref. 3) describe the application of compounds disclosed in Ref. 1 for an anion-selective electrode.

Xiao, K.P. et al. (ref. 4, co-authors are among others Nishizawa and Buehlmann) describe the use of the  
25 bis-thio-ureaxanthene derivative described in ref. 2 in a membrane for a chloride-ion-selective electrode.

All the above-described prior art compounds relate to bis(thio)urea compounds capable of donating four hydrogen bonds for binding negatively charged ions. The  
30 compounds according to the present invention differ from the known compounds in particular in the larger number (6 or more) of hydrogen bonds provided. Despite the fact that negatively charged ions are still bound by maximally four hydrogen bonds from (thio)urea, the compounds according to  
35 the present invention have surprisingly been shown to possess a strong affinity for (dihydrogen) phosphate ions.

According to a favourable embodiment, Y" represents a (thio)urea group, and R4 and R4' an aryl group.

Surprisingly, a compound according to the present invention in which R4 and R4' are aryl sulphonyl, but in particular aryl, has been found to bind two (dihydrogen) phosphate groups, with the phosphate groups interacting together by means of a hydrogen bond. Without the intention of being bound to any theory, it is believed that said interaction leads to an increased affinity constant that was observed.

According to a further favourable embodiment at least one of X and X' is a sulphur atom.

Such compounds were shown to exhibit higher affinity constants for (dihydrogen)phosphate ions.

According to a further favourable embodiment R1 is substituted with two R2 groups.

It has been found that such compounds are better able to bind anions. Without wishing to be tied to any theory, it is believed that the substituents help to prevent mutual interactions between molecules of the compounds according to the invention, such as hydrogen bonds and  $\pi$ - $\pi$  stacks, resulting in hydrogen bonds being no longer available for binding anions. Suitable R2 groups are, for example, isopropyl groups.

A method of preparing an anion-complexing compound with formula I of the formula sheet, wherein a compound selected from the group comprising the compounds VI, VII and VIII of the formula sheet and R2 is as previously defined, is reacted with, in respect of the number of  $\text{NH}_2$  groups, a stoichiometric amount of a compound with the formula IX of the formula sheet, wherein R3 is as previously defined, yielding an intermediate product with the formula X of the formula sheet, with R1 representing the corresponding rest having one of the formulas II, III and IV;

the compound with the formula X is reduced yielding a compound with the formula XI of the formula sheet; and

the compound with the formula XI is reacted with a compound selected from the group comprising  $\text{R5NCX}'$ ,  $\text{R5COCl}$ ,  $\text{R5SO}_2\text{Cl}$ ,  $\text{R6(NCX}')_2$ ,  $\text{R6(COCl)}_2$ , and  $\text{R6(SO}_2\text{Cl)}_2$ ,

wherein R5 represents an aryl which may or may not be substituted with 1 or 2 R3 groups, an alkyl, an acyl and an arylsulphonyl which may or may not be substituted with 1 or 2 R3 groups; and R6 represents a rest selected from the group of a rest with the formula V of the formula sheet, which may or may not be substituted with 1 or 2 R3 groups, and an alkyl group with the formula  $-(CH_2)_n-$  in which n is 2 to 6, yielding a compound with the formula I.

With respect to the last step it is observed that the reaction with an R5-comprising compound results in non-macro cyclic compounds, and those with an R6-comprising compound result in macro cyclic compounds with the formula I.

The invention further relates to an ion-selective membrane comprising a compound according to the invention which is incorporated in a polymeric carrier material.

Such a membrane may be utilized for carrying out separations, analyses, and in particular for sensors. A suitable polymeric carrier material is, for instance, PVC. The compound according to the invention may in accordance with coupling techniques that are known in the art, be coupled to the polymeric carrier material. Alternatively, the compound may also be dissolved in the polymeric carrier material. In particular the groups R2 and R3 could be suitably chosen for this purpose and may, for example, be alkyl.

Therefore the invention also relates to a sensor provided with a compound or a membrane according to the invention.

The sensor itself may be any suitable sensor known in the art, such as an ISFET. The compound may be applied, optionally covalently, to the surface of the sensor, using techniques for coupling molecules to a surface which are generally known in the art.

To the person skilled in the art it will be obvious that the compounds defined in the present application may optionally be substituted with one or more groups that essentially do not change the anion-complexing activity, in other words the affinity and/or the selectivity, of the

compounds. This may, for example, be the case if the compound has to be coupled to a carrier or has to be made compatible with a matrix in which it is to be incorporated. Such compounds fall within the scope of the invention.

The present invention will now be explained with reference to the exemplary embodiments and the illustration below, in which

Fig. 1 represents a reaction scheme for the preparation of compounds according to the invention; and

Fig. 2a, 2b and 2c each show two graphs for a total of three compounds according to the invention. In the left-hand graph the NMR-measured chemical displacement is plotted against the concentration of dihydrogen phosphate. The right-hand graph is a Job-plot of the left-hand graph.

For the preparation of the compounds below, which preparation is schematically illustrated in Fig. 1, and R1, R3, R4, R5, R6, X, X' and Y' have the above definitions, the dimethyl formamide (DMF) used has been distilled in the presence of CaCl<sub>2</sub> and stored over molecular sieves (4 Å). Reactions with (thio)isocyanates were performed under argon.

#### Example 1

Tetrakisurea compound XIII

a) 1,3-bis(methylene(N'-2-nitrophenylureylene))-4,6-diisopropyl-m-xylene

2.3 mmol 1,3-bis(aminomethyl)-4,6-diisopropylbenzene obtained by the method described in ref. 5) is stirred with 2.6 mmol 2-nitrophenyl isocyanate under a dry argon atmosphere for 4 hours in 200 ml dry CH<sub>2</sub>Cl<sub>2</sub>. The precipitated yellow solid was obtained by filtration and dried under vacuum, yielding the title product. Yield 1.0 g (80%). Fusion point 258°C.

Chemical analysis for C<sub>28</sub>H<sub>32</sub>N<sub>6</sub>O<sub>6</sub>

Calculated C: 61.3 H: 5.9 N: 15.3

Found C: 61.2 H: 5.9 N: 15.1

b) 1,3-bis(methylene(N'-aminophenylureylene))-4,6-diisopropyl-m-xylene

The bisnitro derivative was dissolved in a 1:1 mixture of tetrahydrofuran and methanol (100 ml). 0.44 ml hydrazine monohydrate was added as well as a catalytic amount (2.5 g; 50% slurry in water) of Raney nickel, and the solution was refluxed overnight. The solution was filtered over Hyflo (Fluka, Buchs, Switzerland) and the solvent evaporated, yielding the title product. Yield 100%. The product decomposed at 290°C.

Chemical analysis for  $C_{28}H_{36}N_6O_2$ .

10 Calculated C: 68.8 H: 7.4 N: 17.2

Found C: 69.0 H: 7.5 N: 17.4

Tetrakisurea compound XIII

c) to 0.10 g (0.2 mmol) of the diamine obtained in the previous step in 10 ml dry dimethylformamide 0.5 mmol phenylisocyanate is added. The solution is stirred during the night at room temperature. Water is added to eliminate the excess isocyanate and the solution is concentrated by evaporation. The crude product is stirred with methanol. Filtration yielded the title product as white solid.

20 Yield 0.11 g (75%). The substance decomposed at 247°C.

Chemical analysis for  $C_{42}H_{46}N_8O_4 \cdot 0.5 \text{ MeOH}$

Calculated C: 68.7 H: 6.5 N: 15.1

Found C: 68.9 H: 6.5 N: 15.1

#### Example 2

25 Tetrakisurea compound XVII

The method of Example 1 is repeated, except that in step c) propyl isocyanate is used instead of phenyl isocyanate.

Yield 0.08 g (60%). The substance decomposed at 245°C.

30 Chemical analysis for  $C_{36}H_{50}N_8O_4 \cdot \text{MeOH}$

Calculated C: 64.3 H: 7.9 N: 16.2

Found C: 64.6 H: 1.5 N: 16.5

#### Example 3

Tetrakisthiourea compound XIV

35 The steps 2 a) and 2 b) are identical with the steps a) and b) of Example 1.

c) bisurea-bisthiourea compound XIV



This step was identical with step c) of Example 1, while replacing phenylisocyanate with phenylisothiocyanate.

Yield 0.09 g (60%). Fusion point: 163 - 166°C.

5 Chemical analysis for  $C_{42}H_{46}N_8O_2S_2 \cdot MeOH$

Calculated C: 65.3 H: 6.4 N: 14.2 S: 8.1

Found C: 65.1 H: 6.1 N: 14.3 S: 8.3

Example 4

Macro cyclic tetrakisurea compound with the formula XV of  
10 the formula sheet.

Starting with 0.25 g (0.51 mmol) of the product obtained in Example 1 step b), the title compound is obtained by dissolving the starting product in 50 ml dry DMF and adding 0.51 mmol 1,3-bis(isocyanatomethyl)benzene.

15 The solution is stirred overnight, the solvent is evaporated and the crude product is stirred with methanol. After filtering the title product is obtained as a white solid. Yield 0.29 g (85%). The product decomposed at 230°C.

Chemical analysis for  $C_{38}H_{44}N_8O_4$

20 Calculated C: 67.4 H: 6.6 N: 16.6

Found C: 67.7 H: 6.6 N: 16.5

Example 5

Macro cyclic tetrakisurea compound with the formula XVI of the formula sheet.

25 The method described in Example 4 was repeated while replacing 1,3-bis(isocyanatomethyl)benzene with 1,4-diisocyanatobutane. 0.30 g product was obtained (yield 85%) which decomposed at 280°C.

Chemical analysis for  $C_{34}H_{44}N_8O_4$

30 Calculated C: 65.0 H: 7.1 N: 17.8

Found C: 65.2 H: 7.2 N: 18.1

Studies of anion-complexing properties

The ability to bind anions was studied with the aid of 250 MHz  $^1H$ -NMR spectroscopy in dimethylsulphoxide. To  
35 this end 12.5 mmol of a compound according to one of the Examples 1, 2 and 4 were dissolved in 5 ml DMSO-d<sub>6</sub>. A solution of tetrabutyl ammonium salts of  $Cl^-$ ,  $Br^-$ ,  $NO_3^-$ ,  $HSO_4^-$  and  $H_2PO_4^-$  (2.5 mmol per litre) in DMSO-d<sub>6</sub> was added. The observed displacement of a proton of R1 was plotted

against the concentration dihydrogen phosphate (left-hand graphs in Fig. 2). Also, a Job-plot was made based on the measurements.

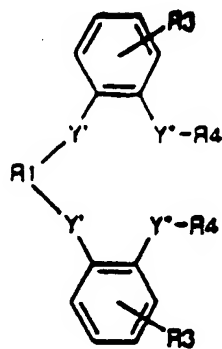
The Job-plot of the  $\text{H}_2\text{PO}_4^-$ -complexing of tetrakisurea compound XIII shows that a maximum complex concentration occurs at a value indicating a ratio of bound  $\text{H}_2\text{PO}_4^-$  : XIII of 1.9. Assuming a 2:1 stoichiometry for the complex, an association constant of  $5 \times 10^7 \text{ M}^{-2}$  is calculated. Such an association constant is the upper limit that can be measured with the aid of the used NMR technique. Neither  $\text{Br}^-$  nor  $\text{NO}_3^-$  or  $\text{HSO}_4^-$  induce a displacement in the NMR spectrum. One equivalent  $\text{Cl}^-$  only results in a small displacement (approximately 0.02 ppm) of the urea protons. The displacements induced by  $\text{H}_2\text{PO}_4^-$  are much greater. Tetrakis thiourea compound XIV gives an association constant comparable with XIII, the upper limit of the method of detection used (not shown).  $\text{Cl}^-$  was shown to bind to XIV at a ratio of 1:1 and the association constant was determined at  $250 \text{ M}^{-1}$ .

Fig. 2b shows that the compound according to Example 2 (XVII, in which R4 is an alkyl group), binds dihydrogen phosphate as a 1:1 complex but also as a 1:2 complex (the Job-plot shows a maximum at 0.56). Due to this it is not possible to accurately calculate an association constant.

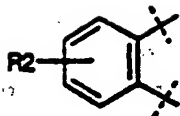
Fig. 2c shows that the macro cyclic tetrakisurea compound XV of Example 4 binds  $\text{H}_2\text{PO}_4^-$  exclusively in a 1:1 stoichiometry. Based on the displacement measured, an association constant of  $2.5 \times 10^3 \text{ M}^{-1}$  was measured. This compound's complexing of  $\text{Cl}^-$  results in a displacement of 0.08 ppm at total complexing for the aromatic urea protons at 7.93 and 7.89 ppm. For  $\text{Cl}^-$  an association constant of  $500 \text{ M}^{-1}$  was calculated.

The macro cyclic tetrakisurea compound XVI of Example 5 is shown to have a comparable binding strength for  $\text{H}_2\text{PO}_4^-$  ( $4.0 \times 10^3 \text{ M}^{-1}$ ), but the binding of  $\text{Cl}^-$  is considerably lower ( $K_a < 50 \text{ M}^{-1}$ ) (not shown). Consequently, the compound according to Example binds 5  $\text{H}_2\text{PO}_4^-$  at least 100 times more selective than  $\text{Cl}^-$ .

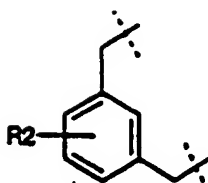
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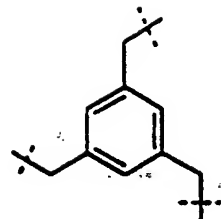
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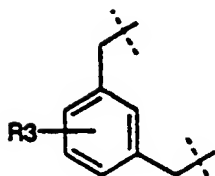
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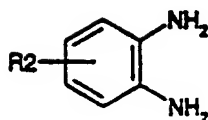
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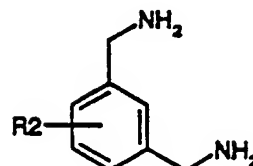
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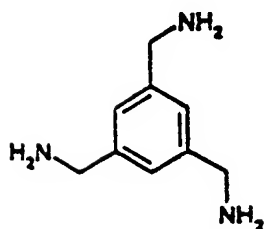
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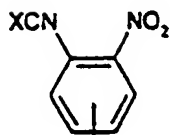
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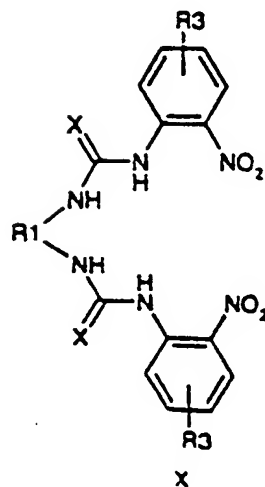
VII



VIII

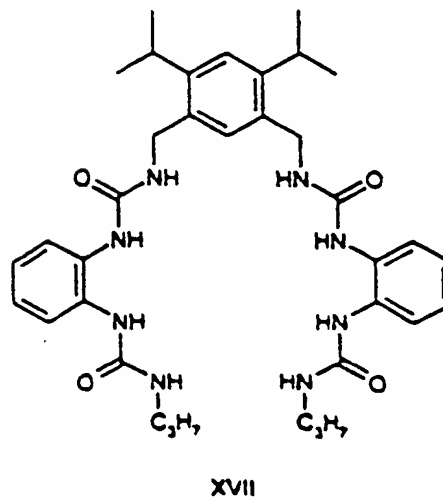
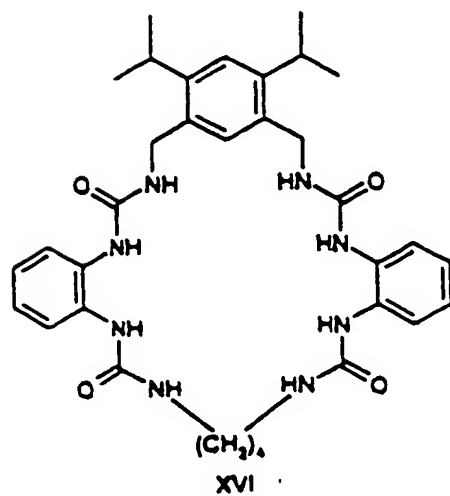
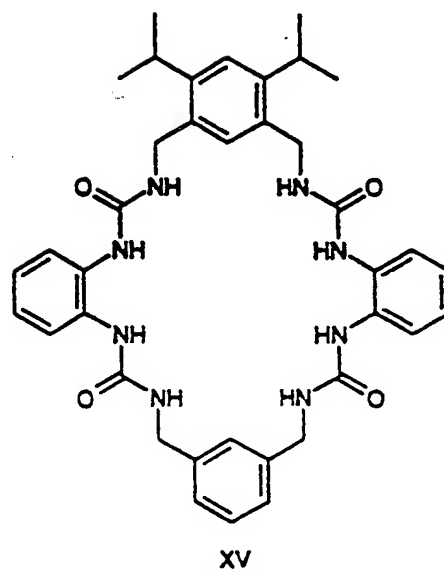
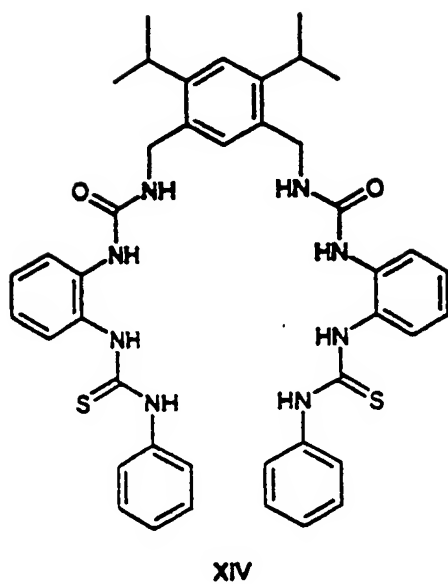
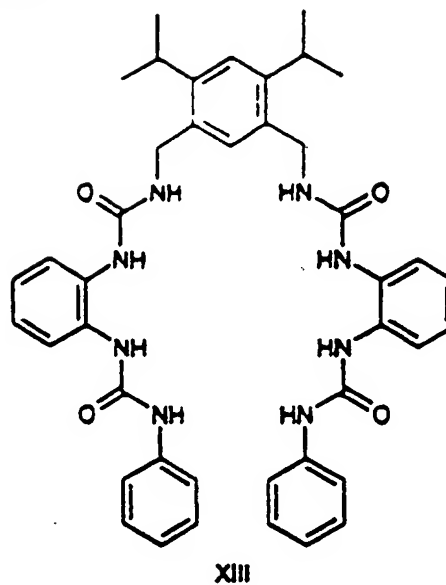
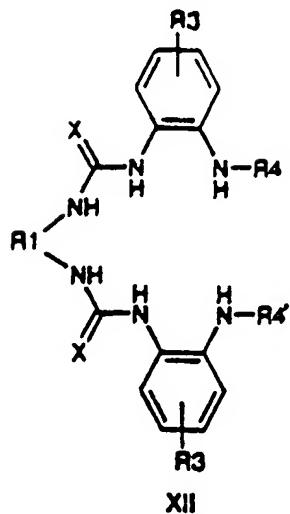
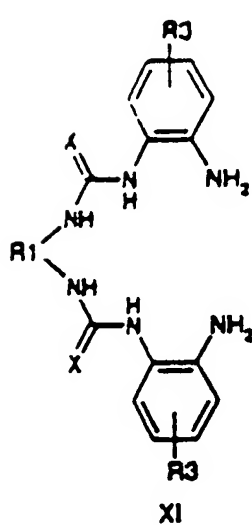


IX



X

## (FORMULA SHEET 2/2)



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CLAIMS

1. An anion-complexing compound with the formula I  
5 of the formula sheet, wherein  
R1 is a rest selected from the group of rests with the  
formulas II, III, and IV of the formula sheet; of which  
the ring may or may not be substituted with 1 to 3 R2  
groups which may or may not be different from each other,  
10 wherein R2 represents alkyl or alkoxy;  
Y' represents a -NHC(X)NH-group, and  
Y" represents a rest selected from the group  
-NHC(X')-, -C(X')NH- and -NHC(X')NH-, wherein  
X and X', independently of one another, represent a  
15 sulphur or oxygen atom;  
A represents an aromatic 6-ring which may or may not  
be substituted with 1 or 2 R3 groups, which R3 groups,  
independently of each other, represent alkyl, alkoxy, NO<sub>2</sub>,  
or a halide selected from the group consisting of fluorine  
20 and chlorine; and  
R4, R4' are either  
a) identical, representing aryl that may or may not  
be substituted with 1 or 2 R3 groups, an alkyl, an acyl  
and an aryl sulphonyl which may or may not be substituted  
25 with 1 or 2 R3 groups;  
or  
b) together form a single rest, which rest is  
selected from the group of a rest with the formula V of  
the formula sheet, which may or may not be substituted  
30 with 1 or 2 R3 groups, and an alkyl group with the formula  
-(CH<sub>2</sub>)<sub>n</sub>- wherein n is 2 to 6.
2. A compound according to claim 1, characterized  
in that Y" represents a (thio)urea group, and R4 and R4'  
an aryl group.
- 35 3. A compound according to claim 1 or 2, character-  
ized in that at least one of X and X' is a sulphur atom.
4. A compound according to one of the preceding  
claims, characterized in that R1 is substituted with R2  
groups.

5. A method of preparing an anion-complexing compound with formula I of the formula sheet, wherein a compound selected from the group comprising the compounds VI, VII and VIII of the formula sheet and R2 is as previously defined, is reacted with, in respect of the number of NH<sub>2</sub> groups, a stoichiometric amount of a compound with the formula IX of the formula sheet, wherein R3 is as previously defined, yielding an intermediate product with the formula X of the formula sheet, with R1 representing the corresponding rest having one of the formulas II, III and IV;

the compound with the formula X is reduced yielding a compound with the formula XI of the formula sheet; and the compound with the formula XI is reacted with a compound selected from the group comprising R5NCX', R5COCl, R5SO<sub>2</sub>Cl, R6(COCl)<sub>2</sub>, R6(COCl)<sub>2</sub>, and R6(SO<sub>2</sub>Cl)<sub>2</sub>, wherein R5 represents an aryl which may or may not be substituted with 1 or 2 R3 groups, an alkyl, an acyl and an arylsulphonyl which may or may not be substituted with 1 or 2 R3 groups; and R6 represents a rest selected from the group of a rest with the formula V of the formula sheet, which may or may not be substituted with 1 or 2 R3 groups, and an alkyl group with the formula -(CH<sub>2</sub>)<sub>n</sub>- in which n is 2 to 6, yielding a compound with the formula I.

6. An ion-selective membrane comprising a compound according to one of the claims 1 to 4 which is incorporated in a polymeric carrier material.

7. A sensor provided with a compound according to one of the claims 1 to 4 or a membrane according to claim 6.

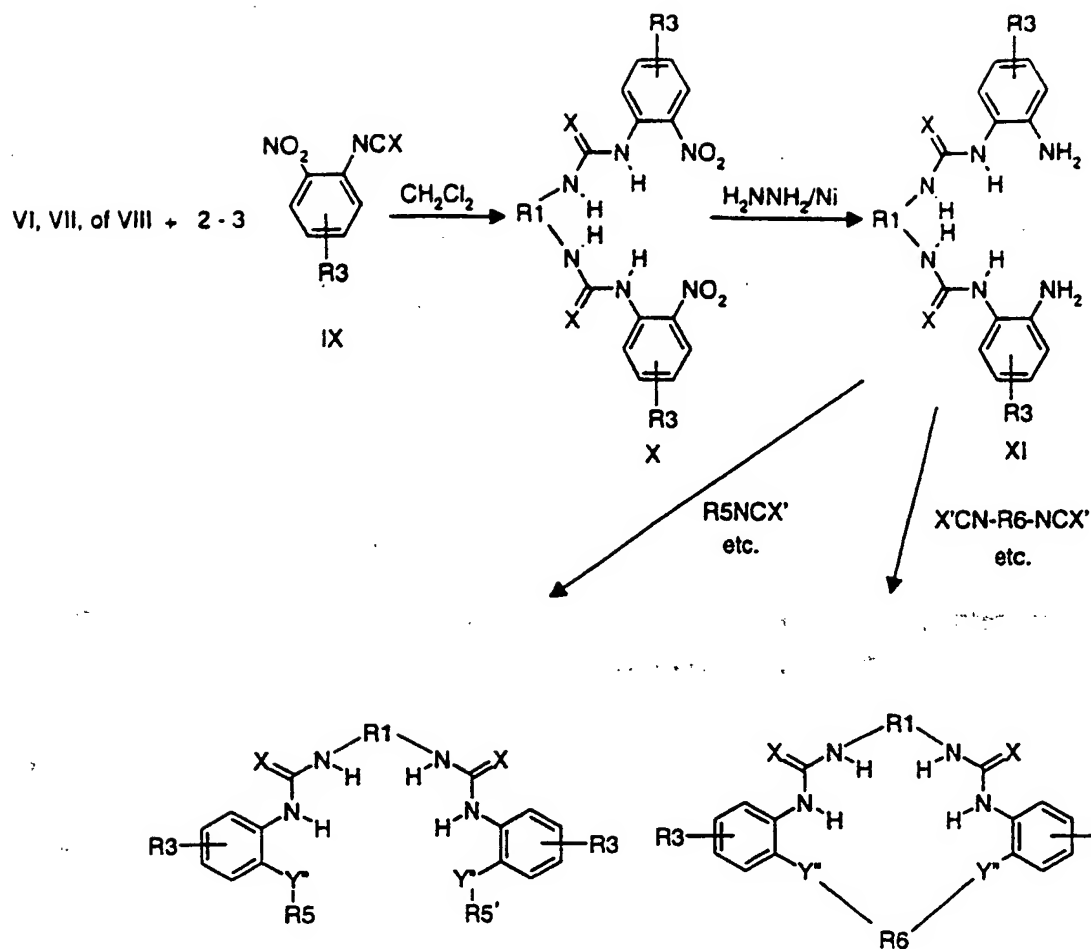
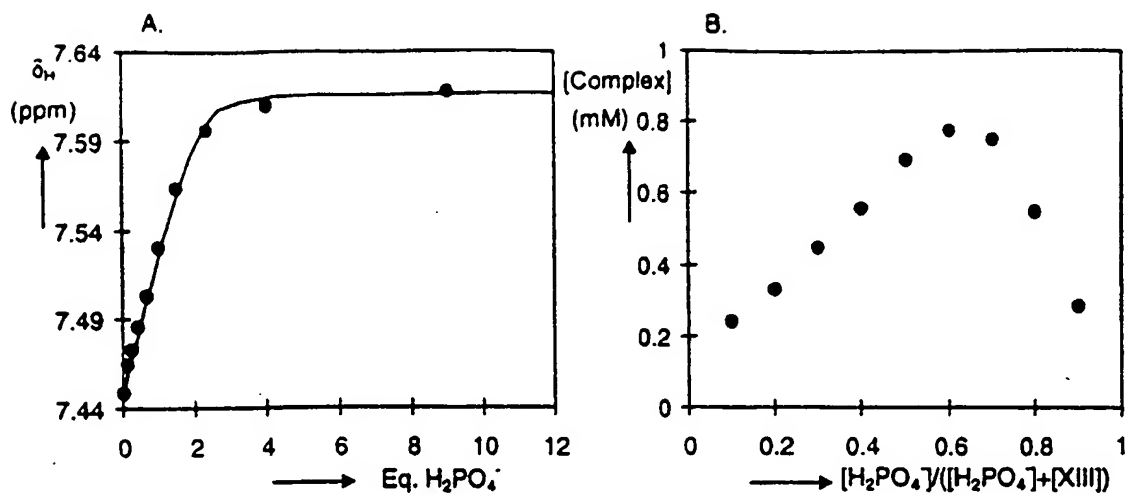


Fig. 1

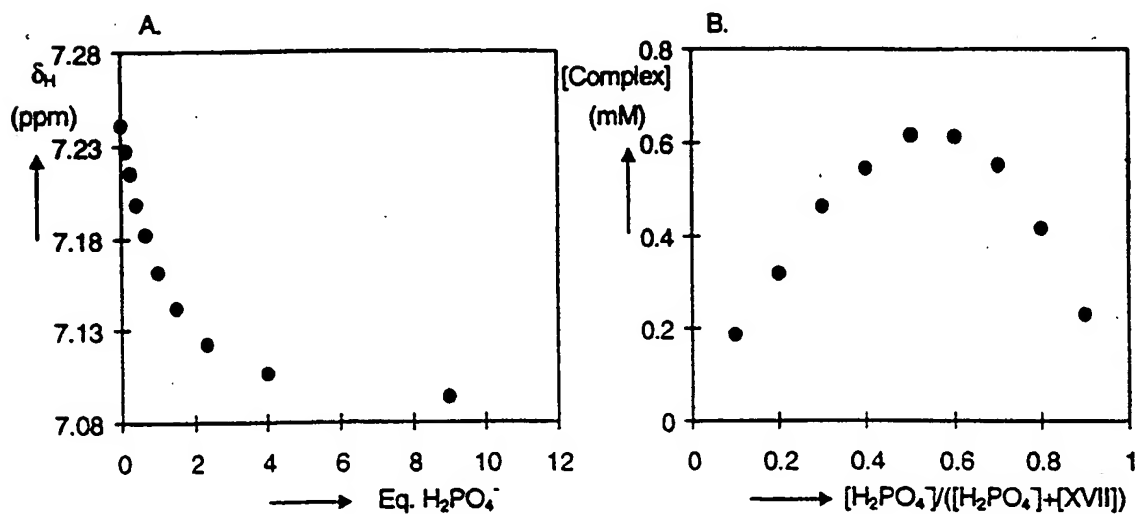


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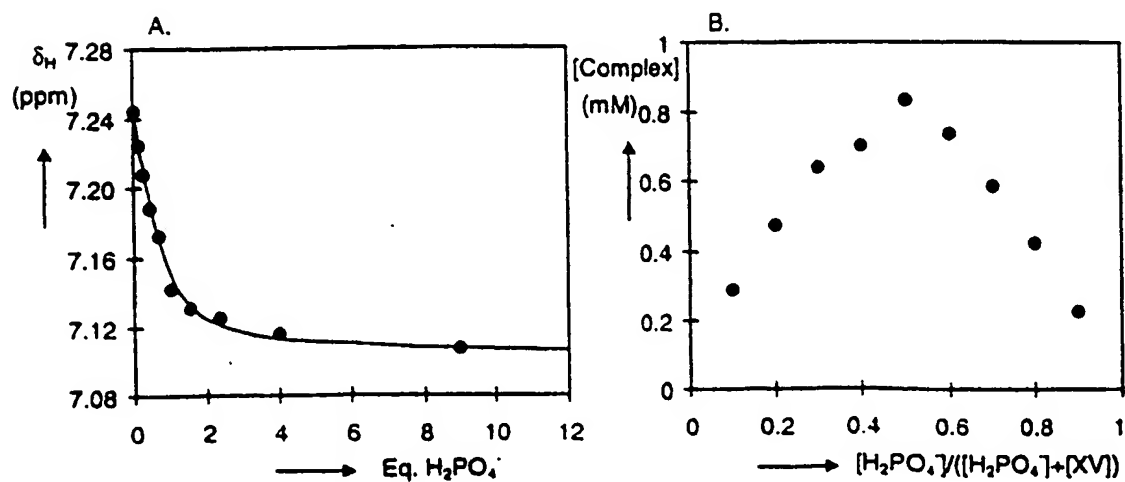
Fig. 2



2a



2b



2c

## INTERNATIONAL SEARCH REPORT

Inte... Application No

PCT 99/00196

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C275/28 C07C335/20 C07D259/00 G01N27/333

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C C07D G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	S. NISHIZAWA, ET AL.: "Application of a bis-thiourea ionophore for an anion selective electrode with a remarkable sulphate selectivity" ANALYTICA CHIMICA ACTA, vol. 358, 1998, pages 35-44, XP002087233 Amsterdam, NL cited in the application see the whole document ---	1,6,7
A	US 5 180 481 A (C. CAREY) 19 January 1993 see the whole document ---	1,6,7
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&amp;" document member of the same patent family

Date of the actual completion of the international search

2 July 1999

Date of mailing of the international search report

12/07/1999

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DATABASE WPI Section Ch, Week 9222 Derwent Publications Ltd., London, GB; Class B05, AN 92-180877 XP002087234 &amp; JP 04 120049 A (SHINGIJUTSU JIGYODAN) , 21 April 1992 see abstract</p> <p>-----</p>	1,67

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Information on patent family members

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		CA 2132704 A	30-09-1993
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		US 5240573 A	31-08-1993
		WO 9319361 A	30-09-1993
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